



Stopped At the Border: Cortical Spreading Depolarization Blocks Seizure Propagation

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Segregation of Seizures and Spreading Depolarization Across Cortical Layers

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Objective: Cortical spreading depolarization (SD) and seizures are often co-occurring electrophysiological phenomena. However, the cross-layer dynamics of SD during seizures and the effect of SD on epileptic activity across cortical layers remain largely unknown. **Methods:** We explored the spatial-temporal dynamics of SD and epileptic activity across layers of the rat barrel cortex using direct current silicone probe recordings during flurothyl-induced seizures. **Results:** Spreading depolarization occurred in half of the flurothyl-evoked seizures. Spreading depolarization always started from the superficial layers and spread downward either through all cortical layers or stopping at the L4/L5 border. In cases without SD, seizures were characterized by synchronized population firing across all cortical layers throughout the entire seizure. However, when SD occurred, epileptic activity was transiently silenced in layers involved with SD but persisted in deeper layers. During partial SD, epileptiform activity persisted in deep layers throughout the entire seizure, with positive signals at the cortical surface reflecting passive sources of population spikes generated in deeper cortical layers. During full SD, the initial phase of SD propagation through the superficial layers was similar to partial SD, with suppression of activity at the superficial layers and segregation of seizures to deep layers. Further propagation of SD to deep layers resulted in a wave of transient suppression of epileptic activity through the entire cortical column. Thus, vertical propagation of SD through the cortical column creates dynamic network states during which epileptiform activity is restricted to layers without SD. **Significance:** Our results point to the importance of vertical SD spread in the SD-related depression of epileptiform activity across cortical layers.

Cortical spreading depolarization (CSD) is a wave of depolarization that spreads slowly over the cortical surface, leaving in its wake a transient state of neuronal inactivity (the latter known as cortical spreading depression). This intriguing pathophysiological phenomenon was initially described by Leão in 1944 while studying the response of rabbit cortex to electrical stimulation.¹ Leão found that in response to a certain pattern of tetanizing electrical stimuli, electroencephalography-recorded cortical activity basically stopped for about a minute and that this wave of depressed cortical activity traveled from the site of stimulation across the cortex at a rate of 3 to 6 mm/min. Subsequent studies have verified the occurrence of CSD in a variety of models and in response to numerous stimuli.² Experimentally, CSD can be elicited by numerous stimuli including mechanical (touching the cortical surface with an object such as a pin), electrical (tetanizing stimuli), or chemical (high potassium, low magnesium, glutamate, and others). Once initiated, the wave of CSD travels over the cortex, involving huge ion fluxes, especially a massive efflux of K⁺ from the intracellular to the extracellular compartments of both neurons and glia. The depression of neural activity that follows CSD is

ultimately a consequence of widespread inactivation of voltage-gated sodium channels. If this inactivation involves a large network of affected neurons, all types of electrical activity in that region of cortex will be depressed. In that regard, the relationship of CSD and seizures is of critical relevance. Theoretically, a seizure might stimulate CSD (as in the case of the present study³) and CSD may counter the excessive electrical activity that occurs during a seizure.

Cortical spreading depolarization is best known as the physiological correlate of migraine aura with aura symptoms correlating with the cortical region affected as the CSD wave passes over the cortical surface. For example, during the time when CSD passes over occipital cortex, a patient may experience visual symptoms such as the illusion of spots, sparkles, or squiggly lines moving across the visual field.⁴ However, CSD is a more widespread consequence of neural injury, and it has also been observed with cerebral ischemia, subarachnoid hemorrhage, and traumatic brain injury.^{2,5-7} If the exact mechanisms of CSD initiation, propagation, and termination could be understood more fully, potential management options could emerge for a wide variety of neurological disorders.



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Though it is well-established that CSD spreads horizontally across the cortical surface, much less is known about its propagation in the vertical extent, that is, from superficial to deeper cortical layers—which cortical layers are necessary or sufficient for CSD propagation and how does this depression of activity affect seizure generation and spread? Such information is important to understand the full spectrum of CSD action, as cellular properties and synaptic function differ among the various cortical layers and thus modulate how electrical activity, including seizure activity, propagates.


The current study addresses these questions straight on. Using a rat model of seizures induced by the inhalant convulsant flurothyl, a γ -aminobutyric acid (GABA) antagonist, Zakharov et al³ used direct current (DC) silicone probe recordings and multiple unit activity recordings to examine electrical activity in the various layers of rat barrel cortex. Rats were immobilized, anesthetized with urethane, and exposed to the inhalant convulsant flurothyl. During a flurothyl-induced seizure, CSD was recorded in about half the seizures. The investigators found that CSD always started in superficial cortical layers and propagated horizontally across the cortical surface, as has been amply documented.⁸ In addition, they found that CSD spreads vertically from the cortical surface down to deeper cortical layers. Interestingly, CSD flows vertically at the same rate at which it flows horizontally. Their pivotal observation was that CSD either involved the entire cortical extent or else stopped at the border between layers IV and V. Moreover, the presence of CSD along the vertical extent of cortex suppressed flurothyl-induced seizure activity in those layers. That is, if CSD involved layers I through IV only, seizure activity would continue in layers V and VI. However, if CSD involved all cortical layers, I through VI, no electrical seizure activity was recorded concurrently. Therefore, it seems that CSD exerts a counter-seizure action, effectively preventing hypersynchronous electrical activity from invading from deep to superficial cortical layers due to the large network of depolarized (and thus inactivated) neurons in superficial layers undergoing CSD. Thus, the border between layers IV and V neurons forms a sort of electrical “barrier” to further CSD vertical propagation.

The study is a technically challenging tour de force. The ability to address these questions is inherently dependent upon the use of DC recordings, as conventional AC recording techniques would filter out the slow CSD waves. Further, the ability to record the all cortical layers allowed comparison of how fast and to what extent the vertically propagating CSD wave proceeds. The abrupt termination of CSD at the layer IV/V border is particularly intriguing and it would be highly informative to determine what membrane or synaptic properties of those respective cells are operative in this phenomenon.


The mechanism by which CSD suppresses seizure activity in response to flurothyl likely relates to flurothyl’s action as a

GABAergic antagonist. Flurothyl does not likely act via a post-synaptic mechanism but rather by affecting GABA release or another presynaptic action.⁹ Therefore, the generalizability of these results needs to be expanded to seizures evoked by means other than flurothyl. It remains to be determined whether CSD interacts with seizure activity in focal-onset seizures similarly to how it acts in generalized seizure models.

These findings are fascinating in their own right, but also point to potential translational importance. Some questions include the following: Could various electrical stimulation techniques or pharmacological approaches currently employed in epilepsy be working, at least partially, via a CSD mechanism? How does seizure activity initiate CSD? Do regions of cortex other than barrel cortex support similar horizontal and vertical CSD propagation? Do animal models differ in their relation of CSD and seizure activity? And perhaps most poignantly, is there any effect of CSD on epileptogenesis and the efficacy of epilepsy treatment? The techniques and ideas in this article provide the substrate to address those questions.

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